Syntex Conference, January 12-13, 1961

1. Discussion with Zaffaroni and Djerassi 1/12/61

Androgenic agents and alkalating agents are being used in combination in the palliative therapy of breast cancer. The impression is that they are being used simultaneously. However, there are some theoretical arguments that this is not the best procedure and it would be preferable to use them in alternation with one another. This would be on the same principle as the antagonism between streptomycin and penicillin in antibacterial therapy since the androgen presumably inhibits the rapid growth of the tumor cells. Such rapid growth in turn is likely to be a necessary condition for the differential susceptability of such cells to the carcinostatic agent. In fact, this would be a useful experimental system for the purpose.

2. Query why dividing cells are in fact more susceptible to radiation and chemical agents. Perhaps this can be attributed to the unique accessability of single-stranded DNA to such agents. The DNA being in a single-strand stage during some part of the division cycle. This in turn is something that can be looked at directly and to some extent, has been, as a byproduct of work in progress on the Subtilis transformation. At any rate, if this is the case, one might use this approach to increase the selectivity of the inhibitory agents. That is to say, those agents would be preferred that had the highest differential in their rate of inactivation of double and of single-stranded DNA.

3. How to increase this differential in situ? At least one should inquire whether one can take advantage of natural rhythms in the mitotic index in order to identify specific times at which the greatest differential would be likely as between various normal tissues of the host and the target tumor. In addition, one might attempt to impose specific synchronization rhythms, for example, by the alternate administration of androgenic and pro-lactogenic agents. This again could be a specific subject for investigation, namely, to determine the variation in sensitivity of such tumor cells depending on their hormonal milieu.

4. Context for discussion of these problems with Kaplan and with George Klein.